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Parental type 2 diabetes in patients with non-affective psychosis

Brian J. Miller [a,*], David R. Goldsmith [b], Nina Paletta [c], Joyce Wong [c], Prianka Kandhal [c], Carmen Black [c], Mark Hyman Rapaport [b], Peter F. Buckley [c]

[a] Department of Psychiatry and Health Behavior, Augusta University, Augusta, GA, USA
[b] Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA
[c] Medical College of Georgia, Augusta University, Augusta, GA, USA

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ABSTRACT

Objective: People with schizophrenia have an increased risk of diabetes that may be independent of antipsychotics. Previous studies have explored the prevalence of a family history of type 2 diabetes (DM2) in schizophrenia. We hypothesized that parental DM2 is increased in probands with non-affective psychosis (NAP) compared to controls, and parental DM2 predicts comorbid diabetes in NAP, after controlling for potential confounders.
Method: N = 217 patients with NAP and N = 67 controls were interviewed for a history of parental DM2. NAP was investigated as a predictor of parental DM2 in binary logistic regression models, controlling for age, sex, race, smoking, body mass index, socioeconomic status, and parental psychiatric history.
Results: There was an increased prevalence of DM2 in the mother (30.0% vs 13.8%, p = 0.013) and in either the mother or father (44.5% vs 24.6%, p = 0.006) in patients with NAP versus controls. After accounting for potential confounders, NAP was associated with significant increased odds of parental DM2 (OR = 2.80, 95% CI 1.08–7.23, p = 0.034). Parental DM2 was also associated with increased odds of comorbid DM2 in NAP (OR = 3.67, 95% CI 1.58–8.56, p = 0.003).
Conclusions: We replicated an association of an increased prevalence of parental DM2 in patients with NAP. Parental DM2 was also an independent predictor of comorbid DM2 in these patients. These associations may be due to shared environmental or genetic risk factors, or gene by environment interactions. Given risks of incident diabetes with antipsychotic treatment, screening for parental DM2 status is germane to the clinical care of patients with NAP.

Dear Editors,

Studies antedating the advent of antipsychotics found an increased prevalence of abnormal glucose metabolism in patients with schizophrenia, although there were methodological limitations (Kohen, 2004). Abnormal glucose tolerance has been observed in antipsychotic-naïve patients with first-episode psychosis (Fernández-Egea et al., 2009), as well as in the relatives of schizophrenia probands (Fernandez-Egea et al., 2008a, 2008b; Spelman et al., 2007). The concept of fetal origins of adult disease posits that events at key time points during gestation impact development and subsequent risk of adult disease (Schlotz and Phillips, 2009), and several risk factors (e.g., birth and maternal factors, and immune genes) are common to schizophrenia and type 2 diabetes (DM2) (Kandhal and Miller, 2013). These findings suggest an increased risk of diabetes in schizophrenia, involving host-agent-environment interactions, that may be independent of antipsychotics. However, this intriguing hypothesis has been largely overshadowed by known metabolic side effects of second-generation antipsychotics (SGAs), which clearly increase the risk of DM2.

Several studies have reported an increased prevalence of a family history of DM2 in schizophrenia probands (Fernandez-Egea et al., 2008b; Mukherjee et al., 1989). The present study investigates associations between parental DM2 and non-affective psychoses. We hypothesized that in probands with non-affective psychosis, there is an increased prevalence of parental DM2, which is also a predictor of comorbid diabetes.

Two-hundred seventeen inpatients and outpatients aged 18–70 diagnosed with schizophrenia (n = 119), schizoaffective (n = 88), psychosis NOS (n = 9), or brief psychotic disorder (n = 1), and 67 controls were recruited in Augusta, Georgia, between July 2010 and November 2015. Exclusion criteria have been reported elsewhere (Miller et al., 2015). Medications were not standardized, although the majority (83%) were treated with SGA monotherapy. After written informed consent, subjects underwent a laboratory (blood draw between 8 and 9 AM after a ten-hour fast), physical and psychiatric diagnostic evaluation. Parental DM2 and psychiatric illness was obtained by self-report. Subjects were diagnosed with DM2 by either self-reported history or a fasting blood glucose ≥126 mg/dL. The study was approved by the IRB's of Augusta University and the Georgia Department of Community Health.

* Corresponding author at: Department of Psychiatry and Health Behavior, Augusta University, 997 Saint Sebastian Way, Augusta, GA 30912, USA.
E-mail address: brmiller@augusta.edu (B.J. Miller).

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Demographic and clinical characteristics were analyzed using either a Chi-square test or Student's *t*-test (2-sided). Binary logistic regression models were used to evaluate subject group as a predictor of a parental DM2, controlling for age, sex, race, BMI, smoking, SES, and parental non-affective psychosis or bipolar disorder. Binary logistic regression models were also used to evaluate parental DM2 as a predictor of DM2 in non-affective psychosis, controlling for the same potential confounding factors. Results were considered statistically significant at the $\alpha = 0.05$ level (two-sided). The data were analyzed using SPSS, version 22.

The Table 1 provides demographic information and regression analyses for the study sample. Data on parental DM2 were missing (unknown/not reported) for n = 35 (16.1%) patients and n = 6 (9.0%) controls. There was a significant increased prevalence of parental DM2 in non-affective psychosis. Results were similar when restricting to subjects with schizophrenia, and subjects without a parental psychiatric history. After controlling for potential confounding factors, we found non-affective psychosis was associated with DM2 in the father (OR = 3.7) or either parent (OR = 2.8), consistent with previous studies (Fernandez-Egea et al., 2008b; Mukherjee et al., 1989). There was also a significant increased prevalence of parental DM2 in subjects with non-affective psychosis and comorbid DM2. In regression, parental diabetes was a significant predictor of comorbid DM2 (OR = 3.7) in non-affective psychosis, also consistent with previous studies (Kusumi et al., 2011; Voruganti et al., 2007). This association underscores that screening parental DM2 status is germane to the clinical care of patients with non-affective psychoses, as it may inform on risk of incident diabetes with antipsychotic treatment.

It is intriguing that in this convenience sample, we found significant associations between non-affective psychosis and parental DM2. We explored parent-of-origin effects, controlled for multiple potential confounding factors, and confirmed DM2 status by both medical history and laboratory testing. An important limitation was that parental DM2 was obtained by self-report only, inducing a potential selective recall bias. It might be expected that patients would be less likely than controls to remember parental history because of greater cognitive impairment; however, our subjects psychosis were more likely to report such a history. In controls, the prevalence of parental DM2 was similar to estimates in this region of Georgia (8.8–11.1%; Georgia Department of Public Health, 2012). Our data do not allow us to determine whether the increased prevalence of parental DM2 is due to shared environmental or genetic factors, or gene-environment interactions. However, our results support the hypothesis that the development of DM2 in non-affective psychosis is multifactorial and not merely a result of SGA use.

Role of funding source

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Contributors

Dr. Miller designed the study. Dr. Miller and Dr. Goldsmith managed the literature searches. Dr. Miller managed the analyses. Dr. Miller wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Miller received grant support for this study from the National Institute of Mental Health (K23MH098014). In the past 12 months, Dr. Miller also received research support from the American Psychiatric Association, National Institutes of Health Clinical Loan Repayment Program and Augusta University; Honoraria from Psychiatric Times; and Speaker fees for lectures from the University of Nevada, Reno.

Dr. Goldsmith has nothing to disclose relevant to the present work. In the past 12 months, Dr. Goldsmith received grant funding from the APIRE-Janssen Resident Research Award and the Janssen Academic Research Mentoring program.

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Ms. Kandhal received funding from the Augusta University Dean's Medical Scholars program.

Dr. Black received funding from the Augusta University Dean's Medical Scholars program.

Dr. Rapaport has nothing to disclose relevant to the present work. In the past 12 months, Dr. Rapaport is a member of the scientific advisory board for Pax, Inc. (unpaid) and the Depression and Bipolar Alternative Therapies Foundation, and a consultant for the American Psychiatric Association.

Dr. Buckley has nothing to disclose relevant to the present work. In the past 12 months, received grant/research support for from the American Psychiatric Association from the National Institute of Mental Health, Janssen Pharmaceutica, Pfizer, and Sunovion, and is a Consultant (Honorarium/Expenses) for the National Institute of Mental Health.

Table 1
Demographic characteristics of the study sample.

	Non-affective psychosis (N = 217)	Controls (N = 67)	p-Value*	OR	95% CI	p-Value
Mean age (±SD)	42.2 ± 12.2	36.5 ± 14.4	*0.004*			
BMI	30.9 ± 8.2	28.6 ± 6.2	*0.032*			
Smoking (cigarettes/day)	7.8 ± 10.5	1.3 ± 3.9	*<0.001*			
SES	32.1 ± 10.7	62.0 ± 18.5	*<0.001*			
Mean paternal age at birth	30.1 ± 9.3	29.1 ± 6.4	0.533			
Mean maternal age at birth	25.8 ± 6.9	25.3 ± 5.2	0.537			
Sex (% male)	59.0	41.8	*0.017*			
Race (%)			*<0.001*			
Caucasian	29.0	46.3				
African descent	68.2	40.3				
East/Southeast Asian	0.0	1.5				
Western Asian	0.0	4.5				
Hispanic	1.4	6.0				
South Asian	0.9	1.5				
Parental DM2 (% yes)						
Either parent (mother, father, or both)	44.5	24.6	*0.006*	2.80	1.08–7.23	*0.034*
Father	23.3	12.9	0.099	4.21	1.16–15.33	*0.029*
Mother	30.0	13.8	*0.013*	2.53	0.84–7.57	0.097

	Non-affective psychosis and comorbid DM2					
	Yes (n = 45)	No (n = 171)				
Parental DM2 (% yes)						
Either parent (mother, father, or both)	67.5	38.0	*0.001*	3.67	1.58–8.56	*0.003*
Father	31.4	21.2	0.261	1.99	0.74–5.35	0.172
Mother	50.0	24.7	*0.003*	3.71	1.56–8.80	*0.003*

Italicized p-values are statistically significant at the $p < 0.05$ level.

* Sex and race were analyzed using the Chi-square test; Student's *t*-test, two-sided, was used for the other comparisons.

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